IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Letters Patent of:
Gentz et al.

Docket No.: PF454P2

Patent No.: 7,285,267

Issued: October 23, 2007

For: Tumor Necrosis Factor Receptors 6 Alpha & 6 Beta

REQUEST FOR CORRECTED PATENT

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Upon reviewing the above-identified patent, Patentee has noticed numerous errors in the printed patent. It is evident that the cause of the errors is that the originally submitted specification rather than the properly submitted substitute specification was used for printing the patent. Patentee respectfully requests that a corrected patent would be more appropriate than a lengthy certificate of correction and that a corrected patent would minimize the potential confusion associated with the patent's disclosure. Further, Patentee notes that a certificate of correction if issued would be approximately seven pages long to properly correct all of the errors, most of which were corrected in the substitute specification filed on October 29, 2003. Finally, in reviewing the issued patent to investigate the reason for the multiple errors, Patentee noticed some additional minor typographical errors that were not corrected in the substitute specification and requests that they be included in the corrected patent.

PATENTEE REQUESTS A CORRECTED PATENT
PURSUANT TO 37 CFR 1.322(b)

37 CFR 1.322 provides:

> (a)(1) The Director may issue a certificate of correction pursuant to 35 U.S.C. 254 to correct a mistake in a patent, incurred through the fault of the Office, which mistake is clearly disclosed in the records of the Office:
>
> * * *
>
> (b) If the nature of the mistake on the part of the Office is such that a certificate of correction is deemed inappropriate in form, the Director may issue a corrected patent in lieu thereof as a more appropriate form for certificate of correction, without expense to the patentee.

35 USC 254 provides:

> Whenever a mistake in a patent, incurred through the fault of the Patent and Trademark Office, is clearly disclosed by the records of the Office, the Director may issue a certificate of correction stating the fact and nature of such mistake, under seal, without charge, to be recorded in the records of patents.... The Director may issue a corrected patent without charge in lieu of and with like effect as a certificate of correction.

As an initial matter, the Patentee respectfully submits that the cause of the mistakes in the printed patent are due to the Patent Office's submitting the original specification instead of the substitute specification for printing. As such, the provisions of 37 CFR 1.322 and 35 USC 254 set forth above are applicable.

Patentee submits that the confusion associated with having the patent in its current form, even with a certificate of correction, would be avoided with a reprinted corrected patent. These errors were corrected in the properly submitted substitute specification on October 29, 2003. The errors include omissions, misnumbered figures and missing tables. Please see the errata set forth below for all of the numerous individual errors. Patentee further submits that with the lengthy certificate of correction that would be necessary to fix the errors, it would be very difficult and confusing for a reader of the patent to properly interpret the disclosure. As such, Patentee requests a corrected patent instead of the issuance of a certificate of correction.

DESCRIPTION OF ERRORS
IN THE PRINTED PATENT

Illustrative of the volume of errors in the patent as published, the corrections that would be necessary in the printed publication are as follows:

On the Title Page:

At Item (54), please correct the Title "Tumor Necrosis Factor Receptors 6α & 6β" to read --Antibodies to Tumor Necrosis Factor Receptors 6α & 6β--.

At Item (56) References Cited-Other Publications, at page 2, reference Bai et al., GenBank Accession No. AF217796, please delete "Feb. 12, 2000" and insert --Feb. 21, 2000--.

At Item (57) Abstract, please delete "polypeptides are also" and insert --polypeptides and antibodies that bind TNFR-6α & 6β polypeptides are also--.

In the Specification:

At page 1, line 38, please delete "TNFR-6α & TNFR-β" and insert --"TNFR-6α, & TNFR-6β"--.

At page 1, lines 41-42, please delete "The invention further relates to screening" and insert --The invention further relates to screening methods for identifying agonists and antagonists of TNFR polypeptide activity. Also provided are diagnostic and therapeutic methods utilizing such compositions.--

At page 3, line 49, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 3, line 59, please delete "niRNAs for TNFR-I and –II (FIG. 3)" and insert --mRNAs for TNFR-I and –II (FIGS. 3A-P)--.

At page 3, lines 65-66, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 6, line 43, please delete "FIG. 2 shows" and insert --FIGS. 2A-B show--.

At page 6, line 47, please delete "FIG. 3 shows" and insert --FIGS. 3A-P show--.

At page 7, line 21, please delete "(FIG. 2)" and insert -- (FIG. 2A)--.

At page 7, line 23, please delete "(FIG. 2)" and insert -- (FIG. 2A)--.

At page 7, lines 45-46, please delete "Fas ligand" and insert --Fas-Fc--.

At page 7, line 56, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 8, line 3, please delete "(FIG. 3)" and insert --(FIGS. 3A-P)--.

At page 8, line 45, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 8, line 50, please delete "(FIGS. 1 and 2" and insert --(FIGS. 1 and 2A-B--.

At page 8, line 55, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 8, line 59, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 9, line 6, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 12, line 20, please delete "FIGS.1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 12, lines 27-28, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 16, line 7, please delete "FIG. 2" and insert --FIG. 2A--.

At page 16, line 17, please delete "TNFR-6□" and insert --TNFR-6α--.

At page 16, line 22, please delete "TNFR-6□" and insert --TNFR-6α and/or TNFR-6β--.

At page 29, line 12, please delete "FIG. 2" and insert --FIGS. 2A-B--.

At page 29, line 31, please delete "FIG. 2" and insert --FIGS. 2A-B--.

At page 30, line 13, please delete "MRNA" and insert --mRNA--.

At page 32, line 29, please delete "FIG. 2" and insert --FIGS. 2A-B--.

At page 32, line 53, please delete "FIG. 2" and insert --FIGS. 2A-B--.

At page 36, line 8, please delete "NSO) and insert --NS0)--.

At page 37, line 9, please delete "pHN-4-5" and insert --pHE4-5--.

At page 48, line 66, please delete "encoding a "FLAG" polypeptide. Thus, a" and insert --encoding a FLAG® polypeptide (DYKDDDDK). Thus, a--.

At page 49, line 1, please delete "FLAG" and insert --FLAG®--.

At page 49, line 6, please delete "pFLAG-CMV-5a or a pFLAG-CMV-1" and insert --pFLAG-CMV™-5a or a pFLAG-CMV™-1--.

At page 49, line 13, please delete "anti-FLAG" and insert --anti-FLAG®--.

At page 50, line 4, please delete "FIG. 2" and insert --FIG. 2A--.

At page 55, line 19, please delete "flag" and insert --FLAG®--.

At page 57, line 34, please delete "FIG. 2" and insert --FIG. 2A--.

At page 64, line 26, please delete "FIG. 2" and insert --FIG. 2A--.

At page 64, line 31, please delete "FIG. 2" and insert --FIG. 2A--.

At page 64, line 33, please delete "FIG. 2" and insert --FIG. 2A--.

At page 65, line 14, please delete "FIG. 2" and insert --FIG. 2A--.

At page 65, line 41, please delete "FIG. 2" and insert --FIG. 2A--.

At page 65, line 45, please delete "FIG. 2 (i.e., SEQ ID NO:2)" and insert --FIG. 2A (i.e., SEQ ID NO:4)--.

At page 65, line 47, please delete "FIG. 2" and insert --FIG. 2A--.

At page 66, line 24, please delete "FIG. 2" and insert --FIG. 2A--.

At page 66, line 31, please delete "FIG. 2" and insert --FIG. 2A--.

At page 87, line 63, please delete "and the "flag" tag." and insert --and the FLAG® tag.--.

At page 125, line 43, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 127, line 11, please delete "FIG. 2" and insert --FIGS. 2A-B--.

At page 127, lines 63-64, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 151, line 23, please delete "anti-FLAG" and insert --anti-FLAG®--.

At page 151, line 26, please delete "anti-FLAG" and insert --anti-FLAG®--.

At page 154, line, 60, please delete "FLAG" and insert --FLAG®--.

At page 154, line 62, please delete "Flag" and insert --FLAG®--.

At page 154, line 64, please delete "Flag" and insert --anti-FLAG®--.

At page 154, line 66, please delete "anti-Flag" and insert --anti-FLAG®--.

At page 155, line 2, please delete "anti-Flag" and insert --anti-FLAG®--.

At page 155, lines 9-10, please delete "(Table IV). Treatment" and insert --(Table V). Treatment--.

At page 155, line 39, please delete "anti-FLAG (200 ng/ml)" and insert --anti-FLAG® antibody (200 ng/ml)--.

At page 155, line 42, please delete "anti-FLAG Mab" and insert --anti-FLAG® antibody Mab--.

At page 165, lines 42-44 please delete "Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models Diabetic Db+/Db+ Mouse Model" and insert the following lines:

--*Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models*

Diabetic db+/db+ Mouse Model--.

At page 174, line 40, please delete "FLAG-FasL+FLAG antibody" and insert --FLAG-FasL+anti-FLAG® antibody--.

At page 174, line, 43, please delete "its FLAG domain" and insert --its FLAG® domain--.

At page 174, line 45, please delete "the FLAG antibody" and insert --the anti-FLAG® antibody--.

At page 174, line 56, please delete "anti-FLAG mouse" and insert --anti-FLAG® mouse--.

At page 174, line 59, please delete "and anti-FLAG" and insert --and anti-FLAG®--.

At page 175, line 7, please delete "with FLAG" and insert --with anti-FLAG®--.

At page 175, lines 22-42, please delete the paragraphs "BIAcoreAnalysis of TR6-Fc.....the presence of TR6-Fc or Fas-Fc." and insert the following paragraphs:

-- *BIAcore analysis of TR6-Fc binding to FasL*

BIAcore chip technology provides the opportunity to identify and characterize ligands that bind to a given receptor, in this case TR6. The protein ligand can be immobilized and challenged with TR6 to calculate relative binding units (RU). Conversely, the TR6 receptor can be immobilized and exposed to various ligands to identify proteins with an affinity for the TR6 receptor.

BIAcore technology was used to determine if human TR6-Fc displayed any binding to human FasL immobilized on a BIAcore chip. The results indicated that TR6-Fc bound to FasL with the same affinity as the Fas receptor, approximately 100 RU. As a control, TR6-Fc interaction with another ligand, BLyS, was examined. No significant binding was found.

To show the specificity of TR6-Fc for FasL, soluble FLAG-FasL was used to compete with the immobilized FasL for binding of TR6-Fc. Increasing concentrations of FasL-Flag were able to inhibit binding of TR6-Fc to immobilized FasL. At a concentration of 8 ug/ml, FasL-Flag inhibited binding of TR6-Fc *2 ug/ml by 50 percent. When 17 ug/ml of Fas-Flag was used, inhibition rose to 75 percent.

When TR6-Fc was immobilized, and trimerized FLAG-FasL used as the soluble protein, the Kd of TR6-Fc was 4.6×10^{-9} M, similar to the 7.4×10^{-9} M Kd for FasFc. TR6 without the Fc portion had a fourfold reduction in affinity for FasL-Flag with a Kd of 1.7×10^{-8} M.—

At page 175, please insert the following paragraphs before lines 43-44:

-- *In vitro effect of TR6 on soluble human FasL mediated cytotoxicity*

The results of this experiment demonstrate the ability of TR6 to block cross-linked FLAG-FasL mediated HT-29 cell death. FLAG-FasL induced HT-29 cytotoxicity in a dose-dependent manner, with a maximal effect at a concentration between 1 and 10 ng/ml. In the

presence of TR6-Fc (1 ug/ml), FasL failed to induce cell killing, in agreement with the proposed decoy receptor function of TR6. Unlike TR6-Fc, Fas-Fc did not totally abrogate FLAG-FasL mediated cell death, but did shift the cytotoxicity curve about 10 fold to the right. TR6-non-Fc also inhibited FasL mediated killing, but was not as potent as the Fc fusion protein. A number of other members of the TNF receptor family, sich as TNFR1-Fc, LTBR-Fc, TR2-Fc, TR4-Fc, TR7-Fc, TR8-Fc, TR9-Fc, TR10-Fc and TR11-Fc were also tested in this assay and failed to block FasL induced killing of HT-29 cells. In a different cytotoxicity assay involving the eponymous TNF family member, TR6-Fc failed to inhibit TNFa-induced killing of L929 target cells.

The ability of TR6 to block antibody cross-linked FLAG-FasL killing *in vitro* was also observed using human Jurkat cells in a similar cytotoxicity assay. Treatment with FasL at 10 ng/ml resulted in an 80% decrease in cell viability as measured by fluorescence at 530/590. Fas-Fc as well as TR6-Fc and non-Fc significantly reduced FasL-induced cytotoxicity whether the decoy receptor level was kept constant and FasL increased, or the FasL level kept constant and the decoy receptor increased. In both assay systems TR6-Fc appeared to be at least 100 fold more potent than Fas-Fc.

In another Jurkat cell assay, treatment with FLAG-FasL resulted in an approximate 7-fold increase in the number of apoptotic cells over untreated controls, as measured by FACS analysis of annexin staining. FasL-mediated apoptosis was significantly reduced in a dose dependant fashion in the presence of TR6-Fc or Fas-Fc.--

At page 176, line 4, please delete "by FLAG" and insert --by anti-FLAG®--.

At page 176, lines 12-13, please delete "of FLAG antibody" and insert --of anti-FLAG® antibody--.

At page 176, line 22, please delete "FLAG antibody" and insert --anti-FLAG® antibody--.

At page 176, lines 29-30, please delete "of FLAG antibody (Table V). This" and insert --of anti-FLAG® antibody (Table VII). This--.

Please delete the paragraph and table beginning at page 176, line 45 through page 177, line 16, and insert the following paragraph and tables:

--To determine if TR6-Fc exhibited protective activity when injected sc, as opposed to iv, 350 ug of TR6-Fc was injected sc, 1.5, 3 or 5 hours before iv injection of 4 ug of FLAG-FasL mixed with 15 ug of anti-FLAG® antibody (Table VIII). Even at the receptor:ligand molar ratio

of 27:1, none of the animals injected sc with TR6-Fc survived for more than two hours, while all of the animals injected iv with 93 ug of TR6-Fc or Fas-Fc survived. A different member of the TNF receptor superfamily, TR-11 (93 ug/mouse, iv) was used as a negative control, and failed to protect any animals from FLAG-FasL induced death. Analysis of blood drawn from mice, injected iv with TR-6-Fc + FasL showed no significant elevation of AST or ALT levels compared to normal controls.

Table VII. Dose dependant effect of TR6-Fc (iv) on cross-linked FLAG-FasL induced mortality

	Time/% Survival				
Groups (n=10) (ug/mouse)	**< 2 Hrs**	**< 4 Hrs**	**1 Day**	**4 Days**	**7 Days**
Normal	100	100	100	100	100
FLAG-FasL (3) + anti-FLAG® Ab (12)	10	10	10	10	10
FasL + Ab + TR6-Fc (2)	0	0	0	0	0
FasL + Ab + TR6-Fc (8)	100	10	10	10	10
FasL + Ab + TR6-Fc (24)	90	80	80	70	70

TR6-Fc and/or FLAG-FasL + anti-FLAG® antibody was injected iv into female Balb/c mice as described in the Material and Methods.

Table VIII. Effect of TR6-Fc (sc, iv) and Fas-Fc (iv) on cross-linked FLAG-FasL induced mortality

	Time/% Survival	
Groups	**< 2 Hours**	**> 24 Hours**
Normal	100	100
FLAG-FasL (4μg/mouse) + anti-FLAG® Ab (15 μg/mouse)	0	0
TR6Fc (350μg/mouse) sc, -5 hr	0	0
TR6Fc (350μg/mouse) sc, -3 hr	0	0
TR6Fc (350μg/mouse) sc, - 1.5 hr	0	0
TR6Fc (93μg/mouse) iv, -1 hr	100	100

Fas-Fc (93µg/mouse) iv, - 1 hr	100	100
TR11-Fc (93µg/mouse) iv, -1 hr	0	0

All groups except normal controls received an iv injection of FLAG-FasL + anti-FLAG® antibody at Time 0.--

At page 182, line 26, please delete "H-2bxd F1 mice" and insert --H-2^{bxd} F1 mice--.
At page 188, line 14, please delete "FLAG tag)" and insert --FLAG® tag)--.

At page 189, line 64, please delete "pFLAGCMV1" and insert --pFLAG-CMV™1--.

At page 191, line 11, please delete "anti-FLAG M2" and insert --anti-FLAG® M2--.

At page 191, line 52, please delete "anti-FLAG M2" and insert --anti-FLAG® M2--.

At page 196, line 52, please delete "(see FIG. 3)".

At page 196, line 54, please delete "; FIG. 3".

Support for the correction of the Title, Abstract and Specification can be found in the Response Under 37 C.F.R. § 111 and Substitute Specification filed by Applicants on October 29, 2003.

The above errors were in the application as filed or amended by Patentees, and thus appear to be the fault of the Patent and Trademark Office. The errors now sought to be corrected do not involve new matter or require reexamination. Accordingly, it is hereby requested that a Corrected Patent under 37 CFR 1.322(b) be issued for the above-identified patent.

While no fee is believed to be due for the application for a corrected patent pursuant to 1.322, if a fee is determined to be due, please charge such fee to our Deposit Account No. 08-3425. Please charge any additional fees due, or credit any overpayment, to our Deposit Account No. 08-3425.

REQUEST FOR CORRECTIONS PURSUANT TO 37 C.F.R. § 1.323

In addition to the mistakes set forth above, Patentees noted the following mistakes that were not in the substitute specification. Patentee requests that these errors be corrected in the corrected patent.

In the Specification:

At page 5, line 1, please delete "has has" and insert --has--.

At page 11, lines 40-41, please delete "FIG.1 or 2" and insert --FIG.1 or 2A-B--.

At page 12, line 10, please delete "FIGS. 1 and 2" and insert --FIGS. 1 and 2A-B--.

At page 13, line 24, please delete "13000," and insert --1300, --.

At page 38, line 31, please delete "CK-□8" and insert --CK-β8--.

At page 43, line 42, please delete "detecable" and insert --detectable--.

At page 53, line 43, please delete "85:5409" and insert --85:5409-5413 (1988),--

At page 50, line 15, please delete "FIG. 2" and insert --FIG. 2A--.

At page 55, line 60, please delete "TNF-alph," and insert --TNF-alpha--.

At page 56, line 22, please delete "are include" and insert --include--.

At page 165, lines 42-44, please delete "Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models Diabetic db+/db+ Mouse Model" and insert the following lines:

-- *Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models*

A. *Diabetic db+/db+ Mouse Model* --.

At page 187, line 1, please delete "testeddid" and insert --tested did--.

At page 196, line 67, please delete "(Table 1)" and insert --(Table IX)--.

At page 197, line 1, please delete "Table 1" and insert --Table IX--.

In the Claims:

In Claim 19(d), please delete "residues the" and insert --residues of the--.

The above mistakes do not appear to be in the application as filed or amended by Patentees. Nonetheless, in light of the request above and Patentee's belief that a corrected patent is appropriate in this case, Patentee respectfully requests that these changes pursuant to 1.323 also be made in the corrected patent rather than in a certificate of correction.

Patentee submits that the above mistakes occurred in good faith, and are either of a clerical or typographical nature, or of minor character. Patentees further submit that the requested corrections neither constitute new matter nor require reexamination.

With respect to the request under 1.323, Patentees hereby authorize the Commissioner to charge the required fee of $100.00, and any other fee deemed necessary, to Deposit Account No. 08-3425, as itemized on the enclosed Fee Transmittal Sheet.

Dated: JANUARY 23, 2008

Respectfully submitted,

By _____

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